

**REMARKS**

Claims 1-11 and 25-34 presently appear in this case. Claims 1-6 have been withdrawn from consideration. No claims have been allowed. The Official Action of August 18, 2006, has now been carefully studied. Reconsideration and allowance are respectfully urged.

Briefly, the present invention relates to filamentous bacteriophage consisting of filamentous bacteriophage that displays an antibody or an antigen-binding fragment thereof. The antibody or fragment binds to an epitope of  $\beta$ -amyloid so as to inhibit aggregation or cause disaggregation of  $\beta$ -amyloid aggregate in the subject. The filamentous bacteriophage may be part of a composition with a carrier, and, in a preferred embodiment, as an active ingredient of a pharmaceutical composition with a pharmaceutically acceptable carrier.

With respect to the election requirement, we note that the examiner has stated that, where applicant elects claims directed to the product and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Accordingly, claims 1-6 remain in the case pending indication of allowability of the product claims and claim 1 has been amended to depend from one of the product claims. It is further noted that the examiner has withdrawn the species election requirement.

The examiner has initialed and returned the previously filed IDS reference lists except that one reference was crossed out as lacking indication of source or date. Attached hereto is a new form listing this reference and including the source and date (as indicated on the paper copy of the reference that the examiner has presumably already considered). Accordingly, initialing of the attached form so that this reference will also be printed on any patent issuing from this case is also respectfully urged.

Claims 7-11 and 25-34 have been rejected under 35 USC 103(a) as being unpatentable over the Solomon PNAS paper and the Hanan and Solomon 1996 paper, as evidenced by Frenkel 1998 and in view of the U.S. patent of Prusiner and Pasqualini 1996. It is essentially the examiner's position that the Solomon and Hanan papers disclose that it was known that  $\beta$ -amyloid peptide could be inhibited and disaggregated by monoclonal antibodies that are directed to the terminal EFRH sequence and that this is further confirmed by Frenkel. The examiner concedes, however, that the primary references do not teach the delivery system of the present invention. For this the examiner cites the Prusiner patent and the Pasqualini publication. The examiner states that Prusiner teaches genetically engineered phages that express a specific binding protein of an antibody on their surfaces, which antibody can be used therapeutically or diagnostically. The examiner states that Pasqualini teaches the targeting of specific tissues, such as the brain, with complete phage peptide libraries and selecting for phage

molecules capable of homing to target tissues *in vivo* and suggests that this method may provide a new means for selective targeting of therapies. Thus, the examiner considers it obvious to display the antibodies of the primary references on the surface of a filamentous bacteriophage, as taught by Prusiner and Pasqualini. This rejection is respectfully traversed.

The combination suggested by the examiner would not have been obvious to one of ordinary skill in the art at the time the present invention was made, in view of the fact that neither Prusiner nor Pasqualini teaches the use of phage displaying any specific antibody as a delivery system. Accordingly, there would have been no motivation to combine Prusiner and/or Pasqualini with the primary references for any purpose.

Prusiner only teaches that combinatorial phage display libraries can be used to identify antibodies. The combinatorial phage display library contains all of the heavy and light Ig chains from an immunized mouse, regardless of antigen-specificity (see col. 23, lines 21-24). This library is used to identify those antibodies that are displayed by the phage and bind to the antigen in question, in the case of Prusiner, prion proteins. However, Prusiner makes it very clear that the antibodies are removed from the phage before they are therapeutically used (see, for example, column 27, lines 6-20, about isolation of soluble Fabs from phage selected from the combinatorial phage display antibody library; see also

column 28, lines 21-45, and Example 6). Nothing in Prusiner is used as a delivery system.

Similarly, Pasqualini does not teach using phage as a therapeutic delivery device. In Pasqualini, an entire phage display peptide library is administered to a mouse in order to find those phages that bind to certain targets, such as the brain. A peptide library is a random combination of amino acids. In other words, an attempt is made to randomly display peptides of a predetermined length that include every possible combination of amino acids. It is not the same as a combinatorial antibody display library, as is used by Prusiner. In Pasqualini, the phage that bind to such targets are then isolated and the homing sequence is then used directly to target tissues. There is no disclosure that phages containing such a homing sequence are ever used therapeutically, i.e., as a delivery system for the specific peptides that are identified by Pasqualini's process. Note that the fourth paragraph of column 1 of Pasqualini states that a soluble cyclic peptide was synthesized according to one of the brain binding phage sequences, and that this peptide inhibited the preferential localization into the brain of the phage carrying the same sequence. Thus, it is apparent that Pasqualini's idea is to find the target-binding phage sequences and then use those sequences as therapeutics, not the phage carrying such a sequence.

Note further the last two sentences of the publication, which state:

As our method selects for molecules capable of homing into target tissues *in vivo*, it may provide a new means for selective targeting of therapies. We have already shown that a peptide synthesized according to a brain-selective phage motif can be used to direct particles (fixed erythrocytes in our experiment) into the brain capillaries.

Thus, as with Prusiner, phage display libraries are only used to identify brain-binding motifs. These motifs are then isolated and used for selective targeting of therapies. There is no suggestion in Pasqualini of the use of a phage bearing such a motif directly as a delivery system for selective targeting of therapies.

This is further evidenced, for example, by patent no. 5,622,699, in which the inventors are the two authors of the Pasqualini publication and which discloses in detail the identification of molecules that home to a selected organ *in vivo* by means of *in vivo* panning, preferably using a phage display library. The organ-homing molecules that are identified by this method are then used for various purposes, but there is no disclosure in the entire patent about therapeutic use of a phage displaying an organ-homing molecule or the use of such a phage displaying a specific organ-homing molecule as a delivery system.

In order to ensure that the present claims do not read on the administration of an entire random phage display library, and, in particular, a combinatorial phage display antibody library, claims 7, 25 and 30 have now been amended to

clarify that the bacteriophage carrying the  $\beta$ -amyloid antibody is the only bacteriophage in the composition.

Accordingly, as no combination of the references of record teach or suggest any motivation for administering a specific antibody while displayed on a filamentous bacteriophage, reconsideration and withdrawal of this rejection are respectfully urged.

It is submitted that all of the claims now present in the case fully comply with 35 U.S.C. §112 and fully define over the references of record. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,  
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